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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,028	DIJKE, ABRAHAM	
	Examiner	Art Unit	
	Arlen Soderquist	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-17 and 27-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-17 and 27-40* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: translations of the three Burdaspal references.

1. Claims 1-10, 12-17 and 27-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1 and 30 paragraph (e), it is not clear if the scope of the aqueous solvent is any aqueous solvent since it includes water which the instant specification defines as a solvent with low PAH solubility, requires some minimum level of water or limits the solution to those defined by claim 9. For examination purposes, the claims will be treated by examiner as requiring sufficient water to be considered an aqueous solution. Additionally in claim 1, it is not clear if the required detection limit can be reached outside of the preferred/disclosed column packing properties, solvents, solvent flow rates and/or PAH detection method (fluorescence). A similar question exists for the detection limit required by claim 40. For examination purposes examiner will treat the claims as not limited to the preferred embodiments disclosed in the specification. With respect to claim 1, this means that examiner is treating the claims as having a scope that is not limited by any of the dependent claims. In claims 27-28, it is not clear if the limitations are further defining steps (d) and (e) of claim 1 of if only step (d) is being further defined. For examination purposes the claims will be treated by examiner as providing a further definition of steps (d) and (e).

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-6, 8-10, 12-17 and 27-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cejpek or Burdaspal (Alimentaria 2001, 38, 117-126, hereinafter referred to as

Burdaspal '01 or Alimentaria 2003, 40, 3-14, hereinafter referred to as Burdaspal '03, translations provided with this action) in view of Williams and Krishen.

In the paper Cejpek presents a simplified extraction and cleanup procedure for the determination of PAHs in fatty and protein-rich matrixes. A simplified analysis procedure for the determination of 12 priority polycyclic aromatic hydrocarbons (phenanthrene, anthracene, fluoranthene, pyrene, benz(a)anthracene, chrysene, benzo(b)fluoranthene, benzo(k)fluoranthene, ***benzo(a)pyrene*** (BaP), dibenz(a,h)anthracene, benzo(ghi)perylene and indeno(1,2,3-cd)pyrene) in meat products and other biological materials has been developed. As a first step, ultrasonic extraction with chloroform (a PAH soluble solvent) for isolation of analytes was used. This is procedure C on page 68. Gel permeation chromatography on Bio-Beads S-X3 utilizing chloroform (a non-aqueous solvent) as mobile phase was applied to remove interferences (lipids, pigments etc.). The paragraph bridging pages 72 and 75 discusses the gel permeation step including the use of THF as mobile phase by prior investigators. The paragraph that follows on page 75 discusses losses of PAHs during the course of the GPC step and recognizes that loss of the more volatile PAH compounds occurs during an evaporation step. HPLC with fluorescence detection was employed for quantitation of analytes. Table 3 shows the variation of the excitation wavelengths for the different compounds. Page 69 teaches that water/acetonitrile mixtures were used in the HPLC determination process. Recoveries at a μg/kg (ppb level) spiking level ranged from 53% (phenanthrene) to 112% (benzo(k)fluoranthrene) with relative standard deviations in the range of 15% (benzo(k)fluoranthene) to 49% (anthracene). Table 7 shows that the recovery of BaP was at least 99%. Figure 5a shows detection of 0.2 μg/kg (0.2 ppb). Table 8 shows that the limits of detection for all of the compounds are less than or equal to 1.0 μg/kg with most being less than or equal to 0.2 μg/kg. The first sentence of page 66 recognizes that the prior art methods are time consuming and cumbersome. The last paragraph of page 78 teaches that the time shortening of procedure C reduces the risk of PAH loss with the main loss attributed to the solvent removing step. Cejpek does not teach the interfacing of the gel permeation chromatography with the HPLC determination apparatus or the use of tetrahydrofuran as the solvent in the gel permeation chromatography process.

In the paper Burdaspal '01 describes an appropriate method for determination of polycyclic aromatic hydrocarbons in pomace olive oil by gel permeation chromatography and

high performance liquid chromatography. This analytical method determines the content of polycyclic aromatic hydrocarbons in pomace olive oil samples by high performance liquid chromatography with fluorescence detection including a previous step to purify the samples by gel permeation chromatography. This method is based and enlarges the scope of a procedure described recently for the specific determination of benzo(a)pyrene in native olive oil and pomace olive oil (Alimentaria, 327, 11-18, 2001). The method has been internally validated for the determination of the eight polycyclic aromatic hydrocarbons specified in the Orden of July 25, 2001, published in the Boletin Oficial del Estado (Spanish Official State Bulletin) ndegree 178 and referred to setting limits for certain polycyclic aromatic hydrocarbons in pomace olive oil: benzo(a)pyrene, benzo(e)pyrene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, dibenzo(a,h)anthracene, benzo(g,h,i)perylene and indeno(1,2,3 - c,d)pyrene. The limit of determination was 0.57 μg/kg (less than 1 ppb) for each hydrocarbon (see tables 1-8 on pages 122-123). Table 9 shows the recovery of the various PAH including over 99% for benzo(a)pyrene. The results of this validation study show the usefulness of this method as a tool to control the presence of those hydrocarbons. Burdaspal '01 does not teach the interfacing of the gel permeation chromatography with the HPLC determination apparatus or the use of tetrahydrofuran as the solvent in the gel permeation chromatography process.

In the paper Burdaspal '03 describes an appropriate analytical method to determine the contents of polycyclic aromatic hydrocarbons in samples of shellfish and fish by high performance liquid chromatography with fluorescence detection including a previous step to purify the crude extracts by gel permeation chromatography. This method is based and enlarges the scope of a procedure described formerly for the specific determination of polycyclic aromatic hydrocarbons in pomace olive oil (Alimentaria, 328, 117-126, 2001). The method has been internally validated for the determination of the eight polycyclic aromatic hydrocarbons specified in the Orden of July 25, 2001, published in the Spanish Official State Bulletin no. 178: benzo(a)pyrene, benzo(e)pyrene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, dibenzo(a,h)anthracene, benzo(g,h,i)perylene and indeno(1,2,3-c,d)pyrene, in fresh mussels and horse mackerel. The limit of determination was at least 0.5 μg/kg (less than 1 ppb) for each hydrocarbon (see tables 1-16 on pages 8-11). Burdaspal '01

does not teach the interfacing of the gel permeation chromatography with the HPLC determination apparatus or the use of tetrahydrofuran as the solvent in the gel permeation chromatography process.

In the paper Williams teaches interface development of a non-aqueous size-exclusion chromatography coupled on-line to reversed-phase high-performance liquid chromatography and applications to the analysis of low-molecular-weight contaminants and additives in foods. An interface has been developed which permits the on-line coupling of size-exclusion chromatography (SEC) in tetrahydrofuran (a non-aqueous solvent) with aqueous reversed-phase high-performance liquid chromatography. The interface isolates the required size exclusion chromatography fraction and dilutes it with water to ensure reconcentration of analytes on the reversed-phase column prior to gradient elution. Operational parameters and the influence of analyte polarity have been examined in detail. A predictive system is presented for determining the applicability of the system to any analyte, based on solute retention times on an ODS phase eluted with a methanol—water gradient. The method is illustrated with examples of direct analyses of crude lipid extracts from a snack product for 2,6-di-tert-4-methylphenol and from chocolate for dibutyl phthalate. Detection limits of ca. 0.5 mg/kg have been achieved. The last full paragraph of page 316 teaches that the application of sequential chromatographic stages (multi-dimensional chromatography) to resolve components of complex mixtures is well known. The method is often carried out off-line (no direct connection between the sequential chromatography stages) but this is not desirable in routine analysis. The paragraph teaches that the online chromatography uses a switching valve to connect the two sequential chromatography stages. The paragraph bridging pages 316-317 teach that size-exclusion chromatography is closely related to gel permeation chromatography, gel permeation chromatography has been applied to lipid cleanup for pesticide analysis and an automated system for this purpose was commercially available. This paragraph also teaches that reverse phase HPLC and size exclusion chromatography offer complimentary advantages. The first full paragraph of page 317 teaches that it is a simple matter to combine size exclusion chromatography with reversed phase HPLC using a column switching technique. The second full paragraph of page 317 discusses the online combination of the two columns. The experimental section on page 317 teaches that the size exclusion material is a poly(styrene-divinylbenzene) material. Figure 1 shoes the system

including a zero dead volume T-piece for adding dilution water and a UV detector. Page 319 under the system development heading teaches that the polystyrene is a preferred material for the size exclusion chromatography to separate lipophilic components from small molecules and that THF is one of a group of effective solvents that also includes toluene and chloroform. This paragraph teaches that 0.5 – 1.0 ml is the typical volume for samples on the standard 7.7 mm SEC column used. The last full paragraph of the page teaches that there is a need to use a solvent as the size exclusion chromatography eluent that is miscible with water. Of the group suitable solvents for the size exclusion chromatography, only THF is a practical candidate. The first full paragraph of page 320 teaches that the SEC peak dilution ratio may be altered as required by varying the THF and water pump flow-rates. Pages 322-323 present an example of how to determine the amount of dilution that might be needed to permit the sample to re-concentrate on the reversed phase column. The last full paragraph of page 323 teaches that any analyte of limited water solubility would be suitable for separation on the coupled system being described. The paragraph bridging pages 323-324 teaches a detection limit of at least 0.5 mg/kg and ways to improve the detection by changing things such as the SEC column length or providing means to allow fluorescent detection.

In the paper Krishen teaches gel permeation chromatography of low molecular weight materials with high efficiency columns. Improvements in the efficiency of small pore packing materials and column preparation have advanced the speed and convenience of gel permeation chromatography to that of gas chromatography and high speed liquid chromatography. Lack of volatility or the absence of significant differences in polarity, solubility, or ionic characteristics, do not pose problems in this technique. A single column, 610 mm × 8 mm, showed a theoretical plate count of 16,000. By using THF as the eluant at a flow rate of 0.5 mL/min, separations in the molecular weight range of 100-2000 were achieved in <30 minutes. A difference of 1 carbon atom was sufficient for satisfactory resolution of components on the lower molecular weight range. This technique was operated with a dual detection system, differential refractive index and UV absorption at 254 nm, to provide additional information. It was applied to low molecular weight entities encountered in the analysis of plasticizers, antioxidants, various condensation products, and other oligomeric species. Figure 4 shows the separation of epoxidized soy bean oil (triglycerides and fatty acids) from other components using

tetrahydrofuran as the eluting solvent. In the experimental section of page 898, the gel used is taught as a polystyrene-divinylbenzene gel.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Cejpek, Burdaspal '01 or Burdaspal '03 in a automated manner as taught by Williams or to modify the process of Cejpek, Burdaspal '01 or Burdaspal '03 by connecting the two chromatography processes into an online process as taught by Williams because of the close relationship between size exclusion chromatography and gel permeation chromatography as taught by Williams, the similarity of the column packing material as shown by Williams and Krishen and the benefits of automation as taught by Williams (providing a way to transfer the solvent between columns without requiring a solvent removal/evaporation step which Cejpek clearly recognizes as the step in which most of the sample losses occur). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use tetrahydrofuran as the elution solvent in the gel permeation separation step of Cejpek, Burdaspal '01 or Burdaspal '03 as taught by Krishen and Williams and modify the flow rates of the solvents used in the dilution step as taught by Williams because of its ability to separate triglycerides from other types of molecules as shown by Krishen and Williams, its water miscibility making it the best solvent for the combined chromatography of lipids as taught by Williams, the fact that the analytes being measured by Cejpek, Burdaspal '01 or Burdaspal '03 are similar to yet different from those measured by Williams and the rapidity of that process as taught by Krishen.

4. Claim 7 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The art of record does not teach or fairly suggest that the first solvent used to dissolve the sample before applying it to the GPC column is a combination of THF and acetonitrile in the proportions claimed

5. Applicant's arguments filed May 16, 2008 have been fully considered but they are not persuasive. First it is noted that Burdaspal '01 and Burdaspal '03 are similar to Cejpek as a primary reference. Each of these references teach a separation and fluorescent measurement of PAHs from the triglyceride/fatty acid portion of an edible oil using a combination of a GPC separation using a non-aqueous solvent followed by a reversed phase chromatography separation

. Thus the comments which follow are appropriate for the combinations based on thus primary references as well. The translations of these references are attached to this office action.

Relative to the arguments that the combination of Williams with Cejpek, Burdaspal '01 or Burdaspal '03 would make the primary references "unsatisfactory for its intended purpose" and/or "change the principle of operation" of the prior art primary references. The following comments are appropriate. Relative to the combination of Cejpek, Burdaspal '01 or Burdaspal '03 with Williams not being proper because it would render the Cejpek, Burdaspal '01 or Burdaspal '03 process unsatisfactory or useless for its intended purpose, examiner notes that, as noted above, Cejpek, Burdaspal '01 or Burdaspal '03 intend to separate and measure the PAH component of edible oils through combining two different chromatographic separation steps. This is done by dissolving the sample in a solvent and applying it to a gel permeation chromatography column and eluting it with a non-aqueous solvent to separate the PAH fraction from the triglycerides and fatty acids in the sample. The PAH fraction is collected and applied to a revered-phase high performance liquid chromatography column and separating with an aqueous solvent/solution prior to fluorescent detection. In each of the primary references the fluorescent detection allows the measurement of the PAH components at a level less than or equal to 1.0 μg/kg. Williams is also trying to separate and measure aromatic components of a lipid (triglyceride) extracted from food (edible) products. In doing this Williams dissolves the sample in a solvent and places it on a size exclusion chromatography column (taught as related to the GCP column in the primary references) and eluting it with a non-aqueous solvent to separate the analytes from the lipids in the sample. The analyte fraction is collected and automatically transferred online to a reversed-phase high performance chromatography column where the analyte is separated and detected. Some teachings of Williams are critical to and provide motivation for the proposed modification. The last full paragraph of page 316 teaches that the application of sequential chromatographic stages (multi-dimensional chromatography) to resolve components of complex mixtures is well known. The method is often carried out off-line (no direct connection between the sequential chromatography stages as found in the primary references) ***but this is not desirable in routine analysis***. This clearly indicates that an online method as taught by Williams would have been an improvement over the off-line methods of the primary references and would have been recognized by one of ordinary skill in the art as a

change that would still allow the primary reference methods to accomplish their intended purpose. In other words, examiner is not merely picking and choosing elements from the reference combination. Furthermore the Cejpek reference clearly teaches the evaporation step associated with the transfer of the PAH fraction to the HPLC column as the primary step for loss of the more volatile PAH molecules. Since Williams replaces this step with an automated transfer that does not involve evaporation of solvent, one of ordinary skill in the art would have expected the modified process of Cejpek, Burdaspal '01 or Burdaspal '03 to have the problem noted by Cejpek.

Relative to the sub-ppb level of detection of PAH, examiner points out that each of Cejpek, Burdaspal '01 or Burdaspal '03 is clearly capable of detection at less than or equal to 1 ppb (1.0 μg/kg). Examiner is not suggesting that the fluorescent detection of the primary references be replaced, rather that the solvent evaporation and manual sample transfer steps be replaced with the automated transfer steps of Williams. How the PAH fraction is transferred to the second column would not change the expectation that the detection limit would be in the sub-ppb range unless there was an expectation that the transfer method would have produced greater loss than that which is expected in the evaporation step. Applicant has not pointed to anything in any of the references that would give an expectation that the sample transfer method of Williams would cause a PAH loss that would exceed that of the evaporation steps of the primary references. Additionally, since the solvent evaporation step, that Cejpek clearly recognizes as the step for loss of volatile PAH molecules, has been eliminated in the Williams reference method, the expectation of a lower detection level for those PAH molecules would have been normal for one of ordinary skill in the art. The detection method of Williams is what limits the detection level to the value taught by Williams. In fact Williams clearly teaches fluorescent detection as a method of possibly enhancing the analyte detection.

Relative to the eluting solvent for the GPC column, Williams clearly considered chloroform and THF as possible solvents for use on the method and chose THF because of its miscibility with water which facilitates the loading of the sample on the HPLC column (page 319). Thus there is, in the teachings of Williams, teachings that would have motivated one of ordinary skill in the art at the time of the invention to use THF as the mobile phase in the GPC in order to combine it with the reversed phase HPLC. Examiner also points out that claim 1 does

not exclude chloroform, toluene or any other solvent in which the PAH are soluble as the first solvent nor does it require the eluting solvent to be the GCP eluting solvent.

Examiner notes that as applicant points out, page 72 of Cejpek discusses the conjugation of the π-electrons with the gel material allowing for the better separation. However it is also clear that the π-electrons are not conjugated with the solvent as it would decrease the separation. One of ordinary skill in the art would have recognized that the conjugation occurs because there are π-electrons in the gel but not in the solvent. That same person of ordinary skill in the art would have recognized that THF does not have π-electrons to have any conjugation effects that would reduce the conjugation between the PAH and the gel. However, Cejpek clearly teaches that the adsorption effect can lead to a higher risk of PAH degradation, and concludes that his procedure with its GPC material provides lower risk of PAH loss due to photooxidative decomposition and sorption capabilities of the PAH because it does not utilize the higher risk adsorption chromatography (page 78, lines 13-20). In other words, the concern in Cejpek was that the use of chloroform with its increased π-electron conjugation or adsorption effect might have increased degradation losses compared to a solvent like THF which has been found by other investigators to reduce the π-electron conjugation or adsorption effect. Since Cejpek teaches that the use of THF has been found to reduce the π-electron conjugation or adsorption effect, it would have been understood by one of ordinary skill in the art that its use would further reduce the loss of PAH due to PAH degradation compared to the use of chloroform as the eluting solvent. Thus the teachings of Cejpek would have also motivated one of skill in the art to the use of THF as the GPC eluting solvent because of its expected reduced risk of PAH degradation losses. This would have added to the clear motivation in Williams to use THF as the GPC eluting solvent compared to chloroform based on its water miscibility properties which Williams considered.

Relative to the dilution ratio and water flushing amounts, examiner points out that they are determined for analytes having polarity equal to or greater than phenol. The PAH molecules are compounds that one of ordinary skill in the art would have recognized as having a polarity that is less than phenol. Thus a reevaluation of the amount of dilution would have been done by the person of ordinary skill in the art. Since PAH are less polar than phenol, they would have

been recognized as requiring less dilution with water than for a more polar substance like phenol. This would surely point one in the direction of the volume of dilution water being approximately equal to the volume of the PAH fraction transferred as required by instant claim 30. It should be further noted that the dilution ratio is not commensurate in scope with the instant claim 1. Additionally the detection limit is not specified for independent claim 30 and so any detection level is acceptable. If applicant wishes to provide probative evidence to show that the dilution ratio of Williams or a dilution ratio based on a calculation of the amount of water needed for analytes that have a polarity of the PAH, as done by Williams for phenol, will not produce the required detection limit of claims 1 or 40, it will be considered along with the requirements that that evidence places on the instantly claimed method.

It should be clearly stated that the detection limit of any method is dependent on at least two factors the detection limit of the detector and the amount of analyte lost from any preparation process required to prepare a sample for detection. In the case of the instant reference combination, as stated above, the modification of the methods in the primary references is not a replacement of the fluorescence detection used with the absorption detector of Williams. Rather it is the automation of the analyte transfer between the two columns. Thus the detection limit of the fluorescence detector has not changed. Any change in the detection limit therefore would be related to changes in the amount of material lost in the steps prior to detection. The art of record clearly shows that THF is a solvent recognized for its ability to separate analytes from lipids in a sample during a GPC separation. Thus there is an expectation that there will be no loss in detection limit due to a change in the GPC eluting solvent to THF. Next, replacing a solvent evaporation step that is clearly recognized as leading to sample loss with a sample transfer that **concentrates** the analyte at the head of the second column would not lead to an expectation of sample loss or a higher detection limit. Finally one would not reduce the purity level of the water based on the teachings of Williams. The detection level that Williams reports cannot be used to show that the detection levels reported by the primary references would be higher because the type of the detector is different from that of the primary references. However, Williams does show a significantly lower detection level than the prior method using the same type of detector since more of the sample is able to be transferred to the second column in the Williams method. Thus there is nothing that applicant can point to that

would lead to an expectation that the detection level of the primary references would be degraded by automating the sample transfer process of the primary references as taught by Williams. Also the reasoning of applicant which does not appear to take into account that the detector type of Williams, UV absorption, is different from the detector type used by the primary references, fluorescence, is not scientifically sound. However as shown above the detection limit is predictable based on the teachings of the applied art and not based on improper hindsight.

The Krishen reference is being relied upon to show that THF is a solvent that is known for lipid/analyte separation on a GPC column and as shown above is not needed for the replacement of the solvent evaporation step of the primary references. Again it is noted that if there are limitations to the process such as types of solvents or limitations on the column materials or sizes that are required to reach the sub-ppb detection level, those features are not now required by claim 1.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art is directed to analysis of PAH, use of gel permeation chromatography and automated transfer of analyte fractions between two chromatography steps.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571)272-1265. The examiner can normally be reached on Monday-Thursday and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Arlen Soderquist/
Primary Examiner, Art Unit 1797